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Hormone replacement therapy, reproductive history, and colorectal adenomas: data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (United States)

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Abstract

Objective: Findings from some epidemiologic studies of colorectal cancer and adenoma suggest that the protective effect of post-menopausal hormone replacement therapy (HRT) may differ across categories of age and body mass index (BMI). We conducted an analysis of women participating in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial to investigate the relationship between HRT use and prevalent adenoma, both overall and across different population subgroups.
Methods: Women aged 55–74 were randomized to screening by flexible sigmoidoscopy at ten PLCO screening centers between September 1993 and September 2001. We identified 1468 women with at least one left-sided adenoma and 19,203 without adenoma or colorectal cancer. Information about HRT and reproductive factors was obtained from a self-administered questionnaire.
Results: Compared to never use of HRT, current use was associated with a decreased prevalence of left-sided adenoma (odds ratio (OR) 0.85; 95% confidence interval (CI) 0.75–0.97). We found no evidence of dose–response with increasing duration of use for current or former users. The association with current HRT use was stronger among women aged 65+ (OR 0.69; 95% CI 0.56–0.84), with a BMI < 30 (OR 0.82; 95% CI 0.71–0.95) and who regularly use aspirin or ibuprofen (OR 0.77; 95% CI 0.65–0.91). Other reproductive factors were not significantly associated with adenoma prevalence.
Conclusions: Our findings suggest that current HRT use may protect against colorectal adenoma, and that this protective effect is short-lived following cessation of use.

Introduction

The relationship between reproductive factors, hormone replacement therapy (HRT) and colorectal cancer has been the subject of considerable study over the past 30 years. Early reports of excess colorectal cancer rates among single women compared with married women [1, 2] and among nuns compared with the general population [3] led McMichael and Potter to suggest that higher parity, early age at first birth and use of exogenous hormones are associated with a reduced risk of colorectal neoplasia [4]. There is now strong epidemiologic evidence supporting a reduced risk of colorectal cancer accompanying recent HRT use [5], including recently published findings from the Women's Health Initiative (WHI), a large randomized controlled trial [6]. These protective effects may occur through estrogen-induced reductions in circulating levels of insulin and insulin-like growth factors [7], or via the inhibition of hypermethylation-mediated silencing of the estrogen receptor gene [8].

The majority of colorectal cancers are believed to arise from colorectal adenomas. Epidemiologic studies of colorectal adenoma can provide valuable insight into

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the early stages of the multi-step process leading to invasive cancer; such knowledge is important for the formulation of effective strategies for disease prevention. A smaller number of studies have investigated whether HRT and reproductive factors are associated with the development of adenomas [9–14]; the findings suggest a reduced risk of adenoma with HRT use but not with other reproductive factors.

There is emerging evidence that the protective effects of HRT use and reproductive factors may be stronger among women who are older [6, 14–16] and thinner [7, 15, 17]. Two studies have also reported a greater reduction in risk with HRT use for larger and more advanced adenomas [13, 18]. However, most of these studies were limited in their ability to investigate such questions of effect modification and etiologic heterogeneity due to sample size constraints.

Data collected as part of the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial offer a unique opportunity to study in detail the relationship between reproductive history, HRT use and colorectal adenoma. Since all study participants had a standardized colorectal cancer screening examination, the issue of differential selection for cases and controls is not of concern as a potential source of bias in this study.

Materials and methods

The PLCO Screening Trial

The PLCO Screening Trial was designed to evaluate the effects of screening on mortality rates for prostate, lung, colorectal, and ovarian cancer among approximately 150,000 US men and women aged 55–74 at enrollment who were randomly assigned to the screening or non-screening arm of the study. Between September 1993 and September 2001, approximately 39,000 women were enrolled and randomized to screening for lung, colorectal and ovarian cancer at screening centers in the following 10 cities: Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St. Louis, MO; and Washington, DC. Details of the PLCO Screening Trial and related protocols for etiologic studies have been published [19, 20].

Women randomized to screening were offered flexible sigmoidoscopy (60 cm) to detect the presence of adenoma, carcinoma and/or other abnormalities in the distal colon and rectum; approximately 75% of women randomized to the screening arm underwent sigmoidoscopy. Those with lesions suspect for colorectal neoplasia (i.e., sigmoidoscopically visualized polypoid lesions or masses) were referred for endoscopic follow-up, including histopathological examination. The PLCO trial obtained all available medical and pathological reports on all lesions removed during the diagnostic endoscopy and related surgical procedures. This information was abstracted and coded by trained medical abstractors. Study participants provided written informed consent, after approval by the institutional review boards of the US National Cancer Institute and the ten screening centers.

A self-completed questionnaire was administered at baseline by all PLCO study participants to ascertain information on a range of potential risk factors for cancer and related diseases. The questionnaire collected information regarding menopausal use of female hormones (ever and current use of tablets, pills, creams) and duration of use; the formulation and dose of hormones were not ascertained. Women recorded their number of pregnancies and live births, age at first live birth, age at menarche and menopause, reason for menopause (natural, surgery, radiation, or drug therapy), use and duration of oral contraceptives, and gynecologic surgeries. Information was also collected on demographic factors, personal and lifestyle characteristics (including height, weight, and exercise), medical history, medication use, previous colorectal cancer screening exams, and family history of cancer. In addition, a 137-item food frequency questionnaire assessed usual dietary intake.

Analytic Data Set

Successful sigmoidoscopic screening examination (insertion to at least 50 cm with $>90\%$ of mucosa visible or a suspect lesion identified) was performed on 29,447 (75%) of the 39,115 women randomized to the screening arm through September 2001. Of these participants, 28,306 (96%) provided information regarding HRT use in the baseline questionnaire. We further excluded 5166 participants who self-reported history of cancer (except basal cell skin cancer), ulcerative colitis, Crohn's disease, familial polyposis, colorectal polyps, or Gardner's syndrome.

After these exclusions, 23,140 participants remained. We excluded participants with distal hyperplastic polyps only (n = 720); with distal benign lesions (n = 125); with colorectal cancer (n = 48); or with adenomas of unknown location or histology (n = 531). We also excluded 1045 subjects with a positive screening for whom pathologic confirmation of colorectal adenoma was unavailable, either because histology data was pending at the time of analysis (n = 49) or because no results from follow-up endoscopy were received (n = 996). Our final study sample consisted of 1468 cases with pathologically verified distal (left-sided) adenomas and 19,203

controls with no suspicion of neoplasia of the distal colon on the sigmoidoscopic screening exam. The data on colorectal adenomas were last updated in August, 2004.

Cases were further characterized according to adenoma location (descending and sigmoid colon, rectum), size (diminutive <0.5 cm, small 0.5–0.9 cm, large ≥ 1 cm), and presence of villous elements. Adenomas were defined as advanced if they were large, had high-grade dysplasia (including carcinoma *in situ*) or had villous elements (including tubulovillous adenomas).

Data analysis

For the purpose of this analysis, HRT was categorized on the basis of status (never, former, current) and duration (0, ≤1, 2–5, 6–9, 10+ years) of use. Reproductive variables included in the analysis were oral contraceptive use (never, ≤1, 2–5, 6–9, 10+ years), parity (0, 1, 2, 3–4, 5+), age at first birth (<20, 20–24, 25–29, 30+), age at menarche (<10, 10–11, 12–13, 14–15, 16+), age at menopause (<40, 40–44, 45–49, 50–54, 55+), reason for menopause (natural, due to surgery/drug therapy/radiation therapy), and history of tubal ligation, hysterectomy, or oopherectomy.

Odds ratios relating these variables to the prevalence of left-sided adenoma were calculated along with corresponding 95% confidence intervals using unconditional logistic regression modeling. Odds ratios were estimated in two ways: adjusting for age at randomization and study center only, and adjusting additionally for other possible confounding factors (ethnicity, education level, marital status, body mass index (BMI), smoking history, aspirin/ibuprofen use, and prior colorectal cancer screening history). Information on physical activity and suspected dietary risk factors for colorectal cancer (consumption of alcohol, red meat, total calcium, total folate, total fat, total fiber) was collected from a separate questionnaire completed by 91% of the participants. Physical activity was adjusted for in multivariate models, with a dummy variable used to define subjects missing these data. Dietary factors were not included in the calculation of multivariate-adjusted odds ratios in order to avoid excluding participants without such data from the multivariate analysis. Additional adjustment for these factors in the subset of participants who completed a dietary questionnaire did not materially affect the odds ratio estimates. Tests for linear trend among ordinal variables were performed using the Wald test by modeling each variable as a single quantitative variable.

Additional models were fit stratifying on selected factors (year of randomization, age at randomization, BMI, ethnicity, physical activity, smoking history, regular use of non-steroidal anti-inflammatory drugs (NSAIDs), family history of colorectal cancer, prior colorectal endoscopy, prior hysterectomy) to investigate whether the associations of HRT use and reproductive factors with adenoma prevalence differ across these categories. Tests of interaction were performed using the likelihood ratio test, comparing models with and without parameters specifying each interaction of interest. Analyses were also performed separately for different adenoma characteristics, including location (descending and sigmoid colon, rectum), size (small, large), presence of villous elements (villous, non-villous), and classification as advanced or non-advanced.

Results

Selected characteristics of the 19,203 women who did not have colorectal adenoma are summarized in relation to their HRT use in Table 1. Current HRT users were younger, better educated and thinner than never users and were more likely to be Caucasian, married, to perform regular exercise, to have used aspirin in the previous year and to have been previously screened for colon cancer. In addition, current HRT users had higher average daily intakes of alcohol, calcium and folate than never users. Former HRT users generally had intermediate levels of these characteristics in comparison to those of current users and never users.

The relationships between left-sided adenoma and HRT use are summarized in Table 2. Current HRT use was associated with a 15% decrease in the odds of having a left-sided adenoma (OR 0.85, 95% CI 0.75–0.97). This association did not materially change upon additional adjustment for dietary factors (OR 0.87, 95% CI 0.76–0.99). No association with former HRT use was apparent. Evidence of a dose–response relationship between the prevalence of left-side adenoma and total duration of HRT use was found, although differences in duration with HRT status appear to explain this finding (10% of former users and 46% of current users reported 10+ years of use). In order to estimate the independent effects of HRT status and duration, a model adjusting for both variables was fit among participants reporting current or former HRT use. Current use was associated with a lower adenoma prevalence than former use, independent of duration (OR 0.82, 95% CI 0.67–0.99); no independent effect for duration was apparent. The association with current HRT use did not materially change when analyses were restricted to women not previously screened for colon cancer, and did not differ for small adenomas (OR 0.79, 95% CI 0.66–0.95) and

Table 1. Distribution of selected variables by HRT user status (never, former, current) among non-cases at baseline screening exam (n = 19,203)

Variable	HRT use		
	% of never users (n = 5995)	% of former users (n = 2891)	% of current users (n = 10,317)
Aged ≥65 years at baseline	41.3	37.1	24.3
Caucasian	85.9	86.7	90.5
College graduate	25.6	27.5	37.2
Currently married	67.6	69.5	75.2
Current smoker	7.8	7.9	5.8
BMI ≥ 30 kg/m^2	29.9	27.1	19.7
No exercise	17.3	15.8	11.6
Regular use of aspirin or ibuprofen during past 12 months	53.0	58.1	61.1
Family history of colorectal cancer in first-degree relative	10.8	10.4	9.4
Ever screened for colon cancer	39.0	42.1	49.2
Alcohol intake ≥5 g/day	21.0	22.4	27.2
Total calcium intake ≥1768 mg/day	20.0	25.1	27.9
Total folate intake ≥808 μg/day	21.1	24.3	27.5
Red meat intake ≥70 g/day	27.2	25.5	23.5
Total fat intake ≥67 g/day	27.3	27.0	24.2
Total fiber intake ≥27 g/day	26.0	27.1	24.2

Abbreviations: n, number; BMI, body mass index; g, gram; mg, milligrams; μg, micrograms; kcal, kilocalories; HRT, hormone replacement therapy.

large adenomas (OR 0.90, 95% CI 0.70–1.17) or for other adenoma characteristics (location, histology; data not shown).

Adenoma prevalence was not associated with oral contraceptive use, age at menopause, reason for menopause, history of gynecologic procedures, parity, or age at first birth (Table 3). Women reporting ages at menarche of less than 10 were more likely to have a left-sided adenoma than those aged 12–13 at menarche, although the 95% CI for this association included unity (OR 1.39, 95% CI 0.93–2.08). The associations with reproductive factors did not materially change when analyses were restricted to women not previously screened for colon cancer, and were not found to differ appreciably with adenoma location, size or histology (data not shown).

Stratified analyses were performed to investigate whether the association between HRT use and left-sided adenoma differed across levels of other participant characteristics; selected results are summarized in Table 4. The inverse effect of current HRT use was stronger among women aged 65+ (OR 0.92, 0.69, 0.68 among age groups 55–64, 65–69, 70–74 respectively). Differential effects with BMI and regular use of NSAIDs were also observed, as the association between current HRT use and adenoma appeared to be restricted to participants with a BMI less than 30 (OR 0.85, 0.80, 0.94 for BMI <25, 25–29, 30+ respectively) and to regular NSAID users (OR 0.77, 0.98 for users and non-users respectively). However, tests for interaction with HRT use were not statistically significant (p = 0.08, 0.65, 0.11 respectively for age, BMI and NSAID use). Neither year of randomization, family history of colorectal cancer, ethnicity, smoking history, physical activity nor prior hysterectomy appeared to modify the relationship between HRT use and adenoma prevalence. The relationships with reproductive factors did not appreciably differ across categories of any participant characteristics.

Discussion

Among women screened for colorectal cancer in the PLCO trial, we found a lower prevalence of left-sided colorectal adenoma in participants who were current users of HRT than in those who were prior users or never users. In addition, the effect of current HRT tended to be strongest among women who were older, non-obese and who regularly used aspirin/NSAIDs. We found no clear relationship between reproductive factors and adenoma, although a non-significant positive association with young age at menarche was observed.

The observation of lower prevalence of colorectal adenoma in HRT users is consistent with five previous studies [9–11, 13, 14]. In small clinic-based case-control studies, Potter *et al.* found HRT use associated with an approximate halving of risk (OR 0.63, 0.43 for <5 years and 5+ year of use, respectively) [9], while Jacobson *et al.* [10] and Peipins *et al.* [11] reported non-significant reductions in risk associated with ever

Table 2. Associations of HRT use with left-sided colorectal adenoma

Variable	Cases n (%)	Non-cases n (%)	Age and center-adjusted		Multivariate adjusted	
			OR	95% CI	OR[a]	95% CI
HRT use						
Never	540 (36.8)	5995 (31.2)	1.00	1.00		
Former	260 (17.7)	2891 (15.1)	1.03	0.88–1.20	1.03	0.88–1.21
Current	668 (45.5)	10,317 (53.7)	0.81	0.72–0.92	0.85	0.75–0.97
HRT duration						
Never	540 (36.8)	5995 (31.2)	1.00		1.00	
≤1 year	166 (11.3)	2086 (10.9)	0.94	0.79–1.13	0.97	0.81–1.17
2–5 years	252 (17.2)	3740 (19.5)	0.87	0.74–1.02	0.93	0.79–1.09
6–9 years	175 (11.9)	2634 (13.7)	0.87	0.73–1.04	0.92	0.76–1.11
10+ years	335 (22.8)	4748 (24.7)	0.83	0.71–0.95	0.85	0.73–0.98
p_{Trend}			0.006		0.03	
HRT use + duration						
Never	540 (36.8)	5995 (31.2)	1.00		1.00	
Former, ≤1 year	130 (8.9)	1499 (7.8)	1.00	0.82–1.22	1.02	0.83–1.25
Former, 2–5 years	77 (5.3)	902 (4.7)	0.98	0.76–1.25	0.97	0.75–1.25
Former, 6–9 years	25 (1.7)	214 (1.1)	1.34	0.88–2.06	1.40	0.91–2.16
Former, 10+ years	28 (1.9)	276 (1.4)	1.09	0.73–1.63	1.05	0.70–1.58
Current, ≤1 year	36 (2.5)	587 (3.1)	0.77	0.54–1.09	0.82	0.58–1.18
Current, 2–5 years	175 (11.9)	2838 (14.8)	0.83	0.69–0.99	0.90	0.74–1.08
Current, 6–9 years	150 (10.2)	2420 (12.6)	0.81	0.67–0.99	0.86	0.70–1.05
Current, 10+ years	307 (20.9)	4472 (23.3)	0.81	0.69–0.94	0.83	0.71–0.97
Restricted to ever users of HRT						
HRT use						
Former	260 (28.0)	2891 (21.9)	1.00		1.00	
Current	668 (72.0)	10,317 (78.1)	0.76[b]	0.63–0.91	0.82[b]	0.67–0.99
HRT duration						
≤1 year	166 (17.9)	2086 (15.8)	1.00		1.00[b]	
2–5 years	252 (27.2)	3740 (28.3)	1.04[b]	0.84–1.30	1.04[b]	0.84–1.31
6–9 years	175 (18.9)	2634 (19.9)	1.09[b]	0.85–1.40	1.08[b]	0.84–1.40
10+ years	335 (36.1)	4748 (36.0)	1.07[b]	0.84–1.35	1.02[b]	0.80–1.30
p_{Trend}			*0.61*		*0.96*	

Abbreviations: n, number; OR, odds ratio; HRT, hormone replacement therapy.

[a] Adjusted for age, ethnicity, PLCO center, education, marital status, smoking, body mass index, physical activity, regular NSAID use and prior screening history.

[b] HRT use and HRT duration adjusted for one another in the same model.

use (OR 0.7, 0.8 respectively). A nested case-control analysis of left-sided adenoma conducted within the Nurses' Health Cohort by Grodstein *et al.* showed lower risks only for large adenoma, among current HRT users (OR 0.74) [13]. Lastly, in a randomized dietary intervention study of individuals with adenomas, Woodson *et al.* found a reduced risk of adenoma recurrence with HRT use among women aged 62+ (OR 0.58), although risks were increased among younger women (OR 1.99) [14].

Our finding of protective effects related to current HRT use is consistent with the report by Grodstein *et al.* [13], while Potter *et al.* found no difference in effect between current and past use [9]. Duration of HRT use was considered in three other studies. Grodstein *et al.* found duration to have no effect on adenoma risk. Potter *et al.* and Peipins *et al.* [11] observed slightly stronger protective effects with greater duration of use. The majority of epidemiologic studies investigating HRT and colorectal cancer have reported stronger effects with current use and an absence of a dose–response relationship with duration [5]. In summary, our findings add to the evidence from several studies suggesting that recent HRT use is an important protective factor for colorectal tumors and that the protective effects may be short-lived following cessation of use.

Table 3. Associations of reproductive variables with left-sided colorectal adenoma

Variable	Cases n (%)	Non-cases n (%)	Age and center-adjusted		Multivariate adjusted	
			OR	95% CI	OR[a]	95% CI
Oral contraceptive use						
Never	722 (49.2)	8527 (44.5)	1.00		1.00	
≤1 year	212 (14.5)	2710 (14.2)	1.08	0.92–1.27	1.06	0.89–1.25
2–5 years	256 (17.5)	3661 (19.1)	1.01	0.86–1.18	1.01	0.86–1.18
6–9 years	116 (7.9)	1784 (9.3)	0.95	0.77–1.18	0.95	0.77–1.17
10+ years	161 (11.0)	2473 (12.9)	0.93	0.78–1.12	0.90	0.74–1.08
p_{Trend}			*0.41*		*0.26*	
Age at menarche						
<10	28 (1.9)	281 (1.5)	1.45	0.98–2.16	1.39	0.93–2.08
10–11	275 (18.8)	3508 (18.3)	1.04	0.90–1.20	1.00	0.87–1.16
12–13	802 (54.7)	10,549 (55.0)	1.00		1.00	
14–15	310 (21.2)	4034 (21.0)	0.99	0.86–1.13	0.98	0.85–1.12
16+	51 (3.5)	812 (4.2)	0.80	0.60–1.08	0.76	0.56–1.02
p_{Trend}			*0.11*		*0.11*	
Age at menopause						
<40	168 (11.5)	2500 (13.1)	0.92	0.77–1.10	0.86	0.71–1.03
40–44	212 (14.5)	2562 (13.4)	1.06	0.90–1.25	1.01	0.86–1.20
45–49	346 (23.7)	4435 (23.3)	1.01	0.88–1.16	0.98	0.85–1.13
50–54	553 (37.9)	7255 (38.1)	1.00		1.00	
55+	179 (12.3)	2311 (12.1)	1.05	0.88–1.26	1.09	0.91–1.31
p_{Trend}			*0.47*		*0.09*	
Reason for menopause						
Natural	961 (66.4)	12,057 (64.0)	1.00		1.00	
Other[b]	486 (33.6)	6787 (36.0)	0.93	0.83–1.04	0.93	0.83–1.04
Any gynecologic surgery						
No	654 (53.1)	7939 (49.5)	1.00		1.00	
Yes	577 (46.9)	8086 (50.5)	0.91	0.81–1.03	0.93	0.83–1.03
Tubal ligation						
No	1173 (80.3)	14,826 (77.5)	1.00		1.00	
Yes	287 (19.7)	4304 (22.5)	0.98	0.85–1.13	0.98	0.85–1.13
Hysterectomy						
No	996 (67.9)	12,679 (66.1)	1.00		1.00	
Yes	472 (32.2)	6498 (33.9)	0.91	0.81–1.02	0.91	0.81–1.02
Oopherectomy						
No	1172 (80.9)	15,386 (81.1)	1.00		1.00	
Yes	277 (19.1)	3587 (18.9)	1.01	0.88–1.16	1.00	0.87–1.15
Parity						
0	140 (9.6)	1766 (9.2)	1.00		1.00	
1	98 (6.7)	1432 (7.5)	0.88	0.67–1.15	0.86	0.65–1.13
2	347 (23.7)	4605 (24.0)	1.01	0.82–1.24	1.02	0.83–1.26
3–4	606 (41.3)	8076 (42.1)	0.94	0.78–1.14	0.96	0.78–1.17
5+	275 (18.8)	3301 (17.2)	0.99	0.80–1.23	0.99	0.79–1.24
p_{Trend}			*0.98*		*0.93*	
Age at first birth						
Nulliparous	140 (9.6)	1766 (9.2)	1.05	0.87–1.27	1.04	0.85–1.27
<20	256 (17.5)	3074 (16.1)	1.19	1.02–1.38	1.09	0.93–1.28
20–24	673 (46.0)	8976 (46.9)	1.00		1.00	
25–29	277 (19.0)	4004 (20.9)	0.89	0.77–1.03	0.92	0.79–1.07
30+	116 (7.9)	1318 (6.9)	1.11	0.90–1.37	1.17	0.95–1.45
p_{Trend}			*0.11*		*0.67*	

Abbreviations: n, number; OR, odds ratio.

[a] Adjusted for age, ethnicity, PLCO center, education, marital status, smoking, body mass index, physical activity, regular NSAID use and prior screening history.

[b] Surgery, drug therapy or radiation therapy.

Table 4. Associations of HRT and left-sided colorectal adenoma, stratified by age at randomization and BMI

Sub-group	HRT use	Cases n (%)	Non-cases n (%)	OR[a]	95% CI	*p* for interaction
Age at randomization						
55–64	Never	256 (29.8)	3519 (26.8)	1.00		0.08[b]
	Former	129 (15.0)	1818 (13.8)	0.99	0.79–1.24	
	Current	475 (55.2)	7814 (59.4)	0.92	0.78–1.09	
65–69	Never	165 (43.5)	1503 (38.7)	1.00		
	Former	80 (21.1)	643 (16.5)	1.12	0.84–1.50	
	Current	134 (35.4)	1742 (44.8)	0.69	0.53–0.89	
70–74	Never	119 (52.0)	973 (45.0)	1.00		
	Former	51 (22.3)	430 (19.9)	1.03	0.72–1.49	
	Current	59 (25.8)	761 (35.2)	0.68	0.48–0.97	
BMI						
<25	Never	186 (32.6)	2127 (26.3)	1.00		0.65[c]
	Former	95 (16.6)	1103 (13.6)	1.05	0.81–1.36	
	Current	290 (50.8)	4865 (60.1)	0.85	0.69–1.04	
25–29	Never	194 (37.7)	2094 (32.0)	1.00		
	Former	91 (17.7)	1010 (15.5)	0.97	0.74–1.26	
	Current	230 (44.7)	3431 (52.5)	0.80	0.65–0.99	
30+	Never	160 (41.9)	1774 (38.8)	1.00		
	Former	74 (19.4)	778 (17.0)	1.10	0.82–1.48	
	Current	148 (38.7)	2021 (44.2)	0.94	0.73–1.21	
Regular use of aspirin of ibuprofen						0.11
No	Never	231 (37.8)	2840 (35.1)	1.00		
	Former	117 (19.2)	1217 (15.0)	1.23	0.97–1.56	
	Current	263 (43.0)	4040 (49.9)	0.98	0.80–1.19	
Yes	Never	309 (36.1)	3155 (28.4)	1.00		
	Former	143 (16.7)	1674 (15.1)	0.90	0.73–1.11	
	Current	405 (47.3)	6277 (56.5)	0.77	0.65–0.91	

Abbreviations: n, number; OR, odds ratio; HRT, hormone replacement therapy; BMI, body mass index.

[a] Adjusted for age, ethnicity, PLCO center, education, marital status, smoking, body mass index, physical activity, regular NSAID use and prior screening history.

[b] Test of interaction performed with age at randomization specified as a dichotomous variable (<65, 65+).

[c] Test of interaction performed with BMI specified as a dichotomous variable (<30, 30+).

Further epidemiologic investigation is needed to clarify the importance of HRT duration and timing.

Concerning the effects of different HRT formulations, a reduced risk of colorectal cancer was observed in the WHI trial of combined estrogen–progestin HRT, but not in the trial of unopposed estrogen (prescribed for women with a previous hysterectomy) [6, 21]. Conversely, case-control studies have not found differences in risk by HRT type [17, 22, 23]. We were unable to directly address this issue, as information on HRT formulation was not collected in PLCO; however, we found no risk differential related to current HRT between women with and without a hysterectomy, suggesting indirectly that the effects of current use are independent of formulation. Further insight into the relevance of formulation may come from a planned analysis that will compare the findings of the two WHI trials in greater detail [21].

We found that protective effects of HRT tended to be strongest in thinner (BMI < 30) and older (aged 65+) women, consistent with several [6, 7, 9, 14–17, 24–26], although not all [6, 13, 17, 27], previous studies. Since adipose tissue is the primary source of estrogen in postmenopausal women [28], HRT has less of an impact on relative estrogen levels in obese women, potentially explaining the weaker effects in this group. Both obesity and estrogen impact circulating insulin and insulin-like growth factor levels [29]; Slattery *et al.* proposed that estrogen and obesity interact in the development of colon cancer through their modulation of the IGF pathway [7]. Estrogen may also have direct anticarcinogenic effects, as demonstrated in colon cancer cell lines [30] and by the recent observation of estrogen receptor (ER) expression in colonic cells [31–34], possibly regulating a variety of cellular functions related to colon carcinogenesis [35–37]. Biologic changes such as increased ER hypermethylation and decreased calcium absorption with increasing age could contribute to age-related modification of HRT's protective action [8, 38, 39].

We also observed the protective effect of HRT to be stronger among women who were regularly using aspirin or ibuprofen, although a test for interaction was not

statistically significant. Use of NSAIDs has been consistently associated with a reduced risk of colorectal cancer and adenoma [40–44]. NSAIDs block the enzyme COX-2 from synthesizing prostaglandins, compounds with pro-carcinogenic effects (enhanced cellular proliferation and angiogenesis and decreased apoptosis) [40]. There is experimental evidence that estrogen increases expression of COX-2 in endothelial tissue [45–47]; however, it is not known whether estrogen similarly influences COX-2 activity in colonic mucosa. Previous epidemiologic studies of colorectal cancer and adenoma, including the WHI trial, have not found evidence of interaction between HRT and NSAID use [6, 9, 15].

Our findings did not differ appreciably with respect to adenoma location, size or other characteristics. By contrast, the study by Grodstein *et al*. found HRT use to be inversely associated with large adenomas only [13]. We did not find clear evidence that reproductive factors earlier in life were related to adenoma prevalence, consistent with most previous reports [9–12, 48]. Our observation that duration of HRT use was not critical also suggests that other hormonal exposures in the past may not be predictive of risk.

Some important strengths of this study include the large number of participants, large number of distal adenoma cases, and the standardized screening procedure for endpoint ascertainment. The analysis was limited, however, by lack of information on formulation and precise time periods of use. Our focus was on left-sided adenoma; generalization of the protective effects of HRT to the entire colon may be underestimates, as some women with no left-sided adenoma probably carry unrecognized right-sided lesions. Women in our study who reported current HRT use differed from never users with respect to several suspected risk factors for colorectal adenoma (Table 1). Such differences raise the possibility that observed reductions in adenoma prevalence with HRT use may be due to the confounding effects of other factors. Our analyses controlled for a variety of colorectal adenoma risk factors that could potentially confound the association with HRT, although we cannot rule out the possibility of residual confounding from these or other unmeasured factors. Because HRT use in our study was related to previous screening history, we carried out sub-analyses showing that HRT was also protective in women who had not had recent screening examinations. The reported findings from the WHI trial of a reduced risk of colorectal cancer accompanying conjugated estrogen–progestin therapy (RR 0.56, 95% CI 0.38–0.81) offer additional support for the argument that the relationship between HRT use and colorectal neoplasia is causal, and not the result of study bias [6].

In conclusion, we found that current HRT use was associated with a reduced prevalence of colorectal adenoma, in particular among post-menopausal women who were older, non-obese and regularly using NSAIDs. Although HRT is not currently recommended for colorectal cancer protection due to other deleterious effects [6], our investigation points to potential tissue-specific targets for colorectal cancer prevention, in steroidal and possibly insulin-like growth factor pathways.

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References

1. Dales LG, Friedman GD, Ury HK, Grossman S, Williams SR (1979) A case-control study of relationships of diet and other traits to colorectal cancer in American blacks. *Am J Epidemiol* **109**: 132–144.
2. Bjelke E (1974) Colorectal cancer: clues from epidemiology. *Excerpta Med Foudation Int Congr* **6**: 324–330.
3. Fraumeni JF Jr, Lloyd JW, Smith EM, Wagoner JK (1969) Cancer mortality among nuns: role of marital status in etiology of neoplastic disease in women. *J Natl Cancer Inst* **42**: 455–468.
4. McMichael AJ, Potter JD (1980) Reproduction, endogenous and exogenous sex hormones, and colon cancer: a review and hypothesis. *J Natl Cancer Inst* **65**: 1201–1207.
5. Grodstein F, Newcomb PA, Stampfer MJ (1999) Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* **106**: 574–582.
6. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, *et al*. (2004) Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* **350**: 991–1004.
7. Slattery ML, Ballard-Barbash R, Edwards S, Caan BJ, Potter JD (2003) Body mass index and colon cancer: an evaluation of the modifying effects of estrogen (United States). *Cancer Causes Control* **14**: 75–84.
8. Issa JP, Ottaviano YL, Celano P, Hamilton SR, Davidson NE, Baylin SB (1994) Methylation of the oestrogen receptor CpG island links ageing and neoplasia in human colon. *Nat Genet* **7**: 536–540.
9. Potter JD, Bostick RM, Grandits GA (1996) Hormone replacement therapy is associated with lower risk of adenomatous polyps of the large bowel: the Minnesota Cancer Prevention Research Unit Case-Control Study. *Cancer Epidemiol Biomarkers Prev* **5**: 779–784.
10. Jacobson JS, Neugut AI, Garbowski GC, *et al*. (1995) Reproductive risk factors for colorectal adenomatous polyps (New York City, NY, United States). *Cancer Causes Control* **6**: 513–518.
11. Peipins LA, Newman B, Sandler RS (1997) Reproductive history, use of exogenous hormones, and risk of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* **6**: 671–675.
12. Platz EA, Martinez ME, Grodstein F, *et al*. (1997) Parity and other reproductive factors and risk of adenomatous polyps of the distal colorectum (United States). *Cancer Causes Control* **8**: 894–903.

13. Grodstein F, Martinez ME, Platz EA (1998) Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Ann Int Med* **128**: 705–712.
14. Woodson K, Lanza E, Tangrea JA, *et al*. (2001) Hormone replacement therapy and colorectal adenoma recurrence among women in the Polyp Prevention Trial. *J Natl Cancer Inst* **93**: 1799–1805.
15. Kampman E, Potter JD, Slattery ML, Caan BJ, Edwards S (1997) Hormone replacement therapy, reproductive history, and colon cancer: a multicenter, case-control study in the United States. *Cancer Causes Control* **8**: 146–158.
16. Prihartono N, Palmer JR, Louik C, Shapiro S, Rosenberg L (2000) A case-control study of use of postmenopausal female hormone supplements in relation to the risk of large bowel cancer. *Cancer Epidemiol Biomarkers Prev* **9**: 443–447.
17. Newcomb PA, Storer BE (1995) Postmenopausal hormone use and risk of large-bowel cancer. *J Natl Cancer Inst* **87**: 1067–1071.
18. Terry MB, Neugut AI, Bostick RM (2002) Risk factors for advanced colorectal adenomas: a pooled analysis. *Cancer Epidemiol Biomarkers Prev* **11**: 622–629.
19. Gohagan JK, Prorok PC, Hayes RB, Kramer BS (2000) The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. *Control Clin Trials* **21**: 251S–272S.
20. Hayes RB, Reding D, Kopp W, *et al*. (2000) Etiologic and early marker studies in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. *Control Clin Trials* **21**: 349S–355S.
21. Anderson GL, Limacher M, Assaf AR, *et al*. (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* **291**: 1701–1712.
22. Persson I, Yuen J, Bergkvist L, Schairer C (1996) Cancer incidence and mortality in women receiving estrogen and estrogen–progestin replacement therapy – long-term follow-up of a Swedish cohort. *Int J Cancer* **67**: 327–332.
23. Troisi R, Schairer C, Chow WH, Schatzkin A, Brinton LA, Fraumeni JF Jr (1997) A prospective study of menopausal hormones and risk of colorectal cancer (United States). *Cancer Causes Control* **8**: 130–138.
24. Jacobs EJ, White E, Weiss NS (1994) Exogenous hormones, reproductive history, and colon cancer (Seattle, Washington, USA). *Cancer Causes Control* **5**: 359–366.
25. Potter JD, McMichael AJ (1983) Large bowel cancer in women in relation to reproductive and hormonal factors: a case-control study. *J Natl Cancer Inst* **71**: 703–709.
26. Hou L, Ji B-T, Blair A (2004) Menopausal modification effect on the association between overweight and colon cancer risk in Chinese women. *J Natl Cancer Inst*.
27. Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW Jr (1995) Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* **87**: 517–523.
28. Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ (2001) Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). *Cancer Causes Control* **12**: 47–59.
29. Yu H, Rohan T (2000) Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst* **92**: 1472–1489.
30. Lointier P, Wildrick DM, Boman BM (1992) The effects of steroid hormones on a human colon cancer cell line in vitro. *Anticancer Res* **12**: 1327–1330.
31. Foley EF, Jazaeri AA, Shupnik MA, Jazaeri O, Rice LW (2000) Selective loss of estrogen receptor beta in malignant human colon. *Cancer Res* **60**: 245–248.
32. Oshima CT, Wonraht DR, Catarino RM, Mattos D, Forones NM (1999) Estrogen and progesterone receptors in gastric and colorectal cancer. *Hepatogastroenterology* **46**: 3155–3158.
33. Hendrickse CW, Jones CE, Donovan IA, Neoptolemos JP, Baker PR (1993) Oestrogen and progesterone receptors in colorectal cancer and human colonic cancer cell lines. *Br J Surg* **80**: 636–640.
34. Singh S, Poulsom R, Hanby AM (1998) Expression of oestrogen receptor and oestrogen-inducible genes pS2 and ERD5 in large bowel mucosa and cancer. *J Pathol* **184**: 153–160.
35. Schwartz B, Smirnoff P, Shany S, Liel Y (2000) Estrogen controls expression and bioresponse of 1,25-dihydroxyvitamin D receptors in the rat colon. *Mol Cell Biochem* **203**: 87–93.
36. Smirnoff P, Liel Y, Gnainsky J, Shany S, Schwartz B (1999) The protective effect of estrogen against chemically induced murine colon carcinogenesis is associated with decreased CpG island methylation and increased mRNA and protein expression of the colonic vitamin D receptor. *Oncol Res* **11**: 255–264.
37. Colin EM, Van Den Bemd GJ, Van Aken M (1999) Evidence for involvement of 17beta-estradiol in intestinal calcium absorption independent of 1,25-dihydroxyvitamin D3 level in the rat. *J Bone Miner Res* **14**: 57–64.
38. Avioli LV, McDonald JE, Lee SW (1965) The influence of age on the intestinal absorption of 47-Ca absorption in post-menopausal osteoporosis. *J Clin Invest* **44**: 1960–1907.
39. Bullamore JR, Wilkinson R, Gallagher JC, Nordin BE, Marshall DH (1970) Effect of age on calcium absorption. *Lancet* **2**: 535–537.
40. Chan AT (2003) Aspirin, non-steroidal anti-inflammatory drugs and colorectal neoplasia: future challenges in chemoprevention. *Cancer Causes Control* **14**: 413–418.
41. Lieberman DA, Prindiville S, Weiss DG, Willett W (2003) Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA* **290**: 2959–2967.
42. Tangrea JA, Albert PS, Lanza E (2003) Non-steroidal anti-inflammatory drug use is associated with reduction in recurrence of advanced and non-advanced colorectal adenomas (United States). *Cancer Causes Control* **14**: 403–411.
43. Sandler RS, Galanko JC, Murray SC, Helm JF, Woosley JT (1998) Aspirin and nonsteroidal anti-inflammatory agents and risk for colorectal adenomas. *Gastroenterology* **114**: 441–447.
44. Martin C, Connelly A, Keku TO (2002) Nonsteroidal anti-inflammatory drugs, apoptosis, and colorectal adenomas. *Gastroenterology* **123**: 1770–1777.
45. Egan KM, Lawson JA, Fries S (2004) COX-2-derived prostacyclin confers atheroprotection on female mice. *Science* **306**: 1954–1957.
46. Tamura M, Deb S, Sebastian S, Okamura K, Bulun SE (2004) Estrogen up-regulates cyclooxygenase-2 via estrogen receptor in human uterine microvascular endothelial cells. *Fertil Steril* **81**: 1351–1356.
47. Akarasereenont P, Techatraisak K, Thaworn A, Chotewuttakorn S (2000) The induction of cyclooxygenase-2 by 17beta-estradiol in endothelial cells is mediated through protein kinase C. *Inflamm Res* **49**: 460–465.
48. Potter JD, Slattery ML, Bostick RM, Gapstur SM (1993) Colon cancer: a review of the epidemiology. *Epidemiol Rev* **15**: 499–545.